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Basis of Cleaning Validation: Setting of PDE Limits

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Cleaning Validation

One of the basic principles of a cleaning validation is the setting of limits for possible cross-contaminants in the subsequent product. The previously used criteria 1/1000 dose and 10 ppm are not based on scientific facts and are no longer to be used as acceptance criteria since the amendment of the GMP regulations. The acceptance criterion "visibly clean" as the sole criterion is no longer acceptable; the previous calculations of the 1/1000 dose criterion and the 10 ppm quantity criterion have been replaced by the science-based Permitted Daily Exposure (PDE) limit. The PDE determination is based on scientific data, such as data generated in toxicological studies, and contains a risk assessment at its core.

Residues of active substances and cleaning agents are considered in the same way. PIC/S Guideline PI 006[1] requires in Chap. 7.9.1: "The efficiency of cleaning procedures for the removal of detergent residues should be evaluated. Acceptable limits should be defined for levels of detergent after cleaning. Ideally, there should be no residues detected. The possibility of detergent breakdown should be considered when validating cleaning procedures."

The method used to date of using the LD50 to calculate the limit value does not correspond to today's standard and the current state of the art. By definition, compliance with the PDE limit value should provide protection in the case of chronic, i.e. daily, exposure. The LD50 results from high dose experiments and describes the lethal dose for 50% of the animals in a study. It is not possible to draw solid conclusions about chronic effects from this.

Principles

All cleaning procedures for equipment whose surfaces come into contact with the product are validated. In this context, equipment is understood to mean all components required for production and primary packaging. This also includes auxiliary equipment (scoops, Müller drums, etc.) that are required during the manufacturing process or sampling.

[1] Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PIC/S PI 006-03, 2007

Cleaning validation includes:

- The derivation of a health-based limit for cross-contaminants (PDE). All substances whose residues may enter a subsequent product are considered on a risk basis. These include:
    - Active ingredients
    - Detergents
    - Potential degradation products

The purification of selected starting materials (e.g. odour- or colour-intensive excipients) is also validated; their limit setting as well as the method for checking the purification success is not part of this SOP.

Annex 15, Chapter 10.6 refers to the requirements of the "EMA PDE Guideline"[2]. This means for a company: In a first step, the PDE values must be determined for all active substances and cleaning agents used, regardless of whether they are assessed as highly toxic or not.

Other starting materials such as odour- or colour-intensive excipients are not explicitly mentioned in the EU GMP Guidelines. As before, their selection is risk-based, e.g. for hygienic or visual reasons. The fact that a substance can be seen or smelled has no bearing on its safety for the patient.

Are other methods for determining threshold values also permitted? The "EMA PDE Guideline" writes in this regard at the outset: "Deviation from the main approach highlighted in this guideline to derive such safe threshold levels could be accepted if adequately justified." However, this sentence in the PDE Guideline should not be taken to mean that thresholds can be waived; rather, it is about the methodology of how they are determined! The main approach presented in the guideline is merely a way to derive such a PDE (i.e., a limit value). In fact, this sentence means: "We need a limit value. How you determine the limit is up to you, as long as you can scientifically justify the value." Here, the PDE guideline allows other methods such as so-called Occupational Exposure-Banding or the concept of Threshold of Toxicological Concern (TTC) to derive such limit values.

- The determination of the critical products for the equipment concerned (identification of the lead substance(s))
- The calculation of the maximum safe carryover (MSC) in the equipment concerned, taking into account the surface in contact with the product
- The identification of critical points of the equipment for sampling

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[2] Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, EMA/CHMP/ CVMP/ SWP/169430/2012

- The sampling and analysis of residues
- The results obtained are used to draw conclusions about the equipment under consideration as a whole.

It is true that according to PIC/S PI 006, chap. 7.3.1 "... only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts into which product may migrate. For example, seals, flanges, mixing shaft, fans of ovens, heating elements etc."

- The head of the area of responsibility (Head of Manufacturing, Head of Quality Control, Head of R&D) is responsible for the cleaning validation.
- Cleaning validation projects are carried out by interdisciplinary teams. These teams are led by the validation coordinator, in close cooperation with the person responsible for the equipment. Depending on the problem, the team includes employees from quality assurance, production, engineering, quality control, microbiology, production planning and more.

In many cases, the validation coordinator (also called validation officer in some companies) and the person responsible for the equipment will be one and the same - person. In any case, however, it is essential to involve the person responsible for the equipment in a cleaning validation project and to make use of his/her expertise.

- For cleaning processes used for dedicated equipment, i.e. product-specific equipment, there is no general validation obligation with regard to active ingredient residues, but the risk of quality impairment due to possible degradation products must be taken into account. In any case, detergent residues and microbiological contamination must be considered.
- There is no validation requirement during preclinical development. The cleaning success is verified by means of decontamination proof, consisting of visual inspection of the cleaning success (visually clean) and, if necessary, a swab test (wipe test).
- The scope of cleaning validation for investigational medicinal products is determined on a risk basis.

The PDE Guideline does not distinguish between early and late phase development. Once GMP is to be applied, a safety assessment of the substance based on the data set available at that time becomes necessary. The excuse "but we have no data" is not sound, because no clinical trial would be approved without data.

In order to be able to derive limit values despite possible data gaps, the toxicologist has several options at his disposal: If available, he can, for example, refer to data of the substance class (read-across) or to initial animal studies and metabolic analyses that are often already available in the early clinical phase. A quantitative structure-activity relationship (QSAR) can be used to derive further indications of the possible toxicological

potential of the substance. In general, experience and toxicological expertise are required when deriving limit values (especially in the case of an incomplete data set).

If the toxicity and efficacy of novel active substances are still insufficiently known at early stages of development, the assessment will initially be correspondingly "conservative" as a result. In the course of development, additional safety-relevant data are collected (animal studies, clinical data). With regard to the safety assessment, it may well be worthwhile to re-evaluate the substance once further study data are available. If necessary, some data gaps can be closed with the new data and thus some uncertainties can be "factored out". It follows: The PDE describes a substance property, but the availability of new data may lead to a completely new assessment.

If the risk assessment results in the opinion that there is a very high risk, then one will generally tend to switch to dedicated equipment (hoses, filters), inliners or campaign production in the small format before starting to swab.

Annex 15 considers in chapter 10.3 the specifics of investigational medicinal products: "It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products, e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use."

The PDE Guideline leaves no doubt that a threshold value is always required, but refers to alternative possibilities of derivation for substances with data gaps compared to the method mentioned in the Guideline. Here, for example, the TTC concept (Threshold of Toxicological Concern) comes into play. However, the choice of methodology should be left to the expert.

The actual cleaning validation in the narrower sense only takes place when moving to pilot or production equipment to produce test preparations in larger quantities (for Phase II and III). The selection of the lead substances is risk-based.

- In order to minimise the investigation effort, bracketing is applied. A justified number of critical products (worst-case products) as well as equipment parts with comparable design are included in the validation, based on the assumption that active substances and equipment in the corresponding groups are comparable.
- As a rule, the cleaning procedure must have been carried out three times in succession, taking into account the maximum service life before cleaning, and must have been classified as successful in order to prove that it is valid.
- The performance of the cleaning validation is subject to the following conditions:
    - The equipment must have a valid qualification (OQ) and be properly maintained and calibrated.
    - Timely training was conducted and documented for personnel who clean or perform cleaning validation activities.
    - The validation plan has been prepared and approved.
    - The analytical methods were validated.
    - Recovery rates were determined.

The training records for all training performed must be available. For the success of a cleaning validation project it is important to train not only the cleaning instructions but also sampling plans, method instructions and all instructions related to cleaning

validation already before the validation is carried out.

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